

棉铃虫对化学杀虫剂的抗性现状及分子机制研究进展

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摘要: 棉铃虫 *Helicoverpa armigera* 是一种世界性分布的重大杂食性农业害虫, 长期大量使用化学药剂防治棉铃虫导致其对不同种类杀虫剂产生了抗性。抗性分子机制的阐明有利于棉铃虫的科学防控和抗性治理。该文主要综述棉铃虫对化学杀虫剂的抗性发展现状, 以及近年来棉铃虫抗药性分子机制的研究进展, 包括解毒酶代谢能力增强、靶标敏感性降低和表皮穿透能力下降等方面, 并就未来研究工作和棉铃虫抗性治理新技术进行了展望。

关键词: 棉铃虫; 抗药性; 分子机制; 抗性治理; 解毒代谢; 细胞色素 P450

Status of resistance to chemical insecticides in cotton bollworm *Helicoverpa armigera* and research progresses on the molecular mechanisms

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Abstract: Cotton bollworm *Helicoverpa armigera* is a serious omnivorous agricultural pest. Long-term and widespread use of insecticides has led to development of resistance in *H. armigera* to a variety of insecticides. Elucidation of the molecular mechanism of resistance is conducive to the scientific control and resistance management of *H. armigera*. This paper reviewed the development of resistance in *H. armigera* to chemical insecticides, and recent research progresses on the resistance molecular mechanisms, including enhanced metabolism mediated by detoxification enzyme, decreased target-site sensitivity, and reduced cuticle penetration. Prospects for future studies and novel control technology of *H. armigera* were also discussed.

Key words: *Helicoverpa armigera*; resistance; molecular mechanism; resistance management; metabolic detoxification; cytochrome P450

棉铃虫 *Helicoverpa armigera* 是一种世界性分布的鳞翅目夜蛾科害虫, 其寄主植物达 200 多种, 可为害棉花、番茄、辣椒、玉米、大豆和马铃薯等多种农作物 (Faheem et al., 2013; Cunningham & Zalucki, 2014)。因其分布广、食性杂、繁殖快和适应性强的特性, 棉铃虫给全球农业造成了巨大的经济损失 (Achaleke & Brévault, 2010; Mironidis et al., 2013; 黄鹏等, 2020)。20 世纪 80 年代末至 90 年代初, 棉铃虫在我国华北和长江流域棉区暴发成灾, 严重为害

棉花及其他多种经济作物 (沈晋良和吴益东, 1995; 郭予元, 1998; 陆宴辉, 2021)。早期棉铃虫的防治主要依赖化学药剂, 但长期大量施用杀虫剂已经导致棉铃虫对不同种类药剂产生了抗性, 其中对拟除虫菊酯类杀虫剂的抗性尤为突出 (夏敬源, 1993; McCaffery, 1998)。1996 年转 Bt 基因抗虫棉花 (简称 Bt 棉花) 开始在全球范围内种植, 并于次年在我国推广。随着 Bt 棉花的广泛种植, 棉铃虫得到了有效控制, 其在棉田的发生量有所减少, 但在玉米以及

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番茄等其他作物上却逐年增多(Wu et al., 2002; Wu & Guo, 2005)。此外,长期种植Bt棉花已导致棉铃虫对Bt蛋白产生了抗性,吴益东等(2021)对其抗性现状和分子机制进行了综述。Bt棉花的种植还使Bt棉田杀虫剂的使用模式发生了变化,导致为害棉花的其他害虫,如盲蝽(Lu et al., 2010)、棉蚜 *Aphis gossypii* (王风延等, 2003; 徐文华等, 2008; 吕丽敏等, 2013)等随之增加。迄今为止,施用化学杀虫剂仍然是防治棉田其他害虫以及玉米、番茄等作物上棉铃虫的主要手段。棉铃虫对化学杀虫剂的抗性并未因Bt棉花的种植而消失,其抗性治理仍是当前农业生产中亟待解决的问题。

阐明害虫抗药性分子机制是抗性治理的前提,可为害虫综合防治提供理论依据。本文主要针对棉铃虫对化学杀虫剂的抗性发展概况,并结合近年来该虫抗药性分子机制的研究进展,尤其是细胞色素P450酶系介导的代谢能力增强等方面进行综述,以期对棉铃虫抗性治理和有效防控提供参考依据。

1 棉铃虫对化学杀虫剂抗性发展概况

1.1 国外棉铃虫抗药性发展概况

自20世纪70年代初开始,国外就已报道棉铃虫对滴滴涕产生了高水平抗性,抗性倍数达几十倍甚至上百倍(Wilson, 1974; Ahmad & McCaffery, 1988)。最早是由Gunning et al. (1984)报道澳大利亚昆士兰州棉区棉铃虫对氯氰菊酯、溴氰菊酯和氰戊菊酯等拟除虫菊酯类杀虫剂产生了15~30倍的抗性,从而引起广泛关注。在欧洲,棉铃虫抗药性问题同样不容忽视。2000—2001年,法国南部番茄种植区棉铃虫对溴氰菊酯表现出中等水平抗性,抗性倍数为11.5~32.4倍(Bués et al., 2005)。2004年西班牙棉区棉铃虫对硫丹产生了11.4倍的抗性(Avilla & González-Zamora, 2010)。2010年以前,希腊北部棉铃虫抗药性水平尚处于敏感或低水平抗性,但在2010年,棉铃虫对毒死蜱和 α -氯氰菊酯的抗性倍数分别上升到45.79倍和80.89倍(Mironidis et al., 2013)。21世纪初期,在亚洲南部也监测到棉铃虫出现不同程度的抗药性。如在2005—2007年,印度哈里亚纳田间棉铃虫对氯氰菊酯表现出高水平抗性,抗性倍数高达130.978倍;对灭多威产生中等水平抗性,抗性倍数为18.345倍(Bajya et al., 2011)。2009—2012年,巴基斯坦棉铃虫对联苯菊酯、三氟氯氰菊酯和溴氰菊酯产生中等至高水平抗性,抗性倍数分别为34.1~48.0倍、19.6~68.2倍和19.3~37.2倍;

对丙溴磷和毒死蜱的抗性倍数为24.57~116.50倍和22.65~87.07倍;对甲氧虫酰肼和硫双威的抗性倍数分别为6.0~11.8倍和5.6~11.5倍(Hussain et al., 2015; Qayyum et al., 2015)。2014—2015年,非洲塞内加尔11个棉铃虫田间种群对溴氰菊酯表现为中等至高抗水平,抗性倍数为10.7~111.9倍,表明该国棉铃虫田间种群普遍对溴氰菊酯产生了抗性(Sene et al., 2020)。

1.2 国内棉铃虫抗药性现状

我国棉花种植区主要包括华北棉区、长江流域棉区和新疆维吾尔自治区(简称新疆)棉区。其中华北和长江流域棉区受害较严重,棉铃虫对杀虫剂的抗性最为突出。项海兰(2009)在2000—2008年监测发现湖北省棉铃虫田间种群对高效氯氰菊酯具有高水平抗性。Xu et al. (2016)在2013—2014年测定了我国北方棉田棉铃虫的抗性水平,结果发现河南省安阳市、河北省河间市、北京市、山东省潍坊市和夏津县棉铃虫田间种群对氰戊菊酯具有中等至高水平抗性,抗性倍数为55.8~114.7倍。Wang et al. (2021)调查报道,2017年河南省和山东省等华北棉区棉铃虫对茚虫威、丁硫克百威、甲氧虫酰肼、氯虫苯甲酰胺、氰氟虫腙和高效氯氟氰菊酯产生中等水平抗性,抗性倍数最高分别为28.43倍、24.29倍、29.57倍、35.28倍、17.09倍和33.54倍。胡红岩等(2018; 2021)研究报道,河南省、河北省、山东省和山西省等华北棉区棉铃虫田间种群对辛硫磷产生了中等至高水平抗性,在不同年份其抗性倍数也不同,2014—2015年为13.0~58.5倍,2016年为25.2~65.7倍,2017年为24.2~48.8倍,2018—2019年为21.1~55.3倍;对三氟氯氰菊酯表现出中等至高水平抗性,抗性倍数为14.1~269.3倍,而且抗性水平整体呈现逐年上升趋势,2014年、2015年、2016年、2017年、2018年和2019年抗性倍数分别为14.4~61.0倍、29.8~101.9倍、21.3~165.7倍、72.3~269.3倍、65.2~134.1倍和44.7~216.3倍,其中山东省夏津县棉铃虫田间种群的抗性水平上升最明显,抗性倍数高达269.3倍;对甲氨基阿维菌素苯甲酸盐表现为低至中等水平抗性,抗性倍数为5.5~92.8倍。王冬梅等(2020)监测到新疆棉铃虫田间种群对三氟氯氰菊酯和氯虫苯甲酰胺均已产生中等水平抗性,抗性倍数分别为10.79倍和10.62倍。在我国东北地区也监测到了抗性棉铃虫,如沈阳市棉铃虫田间种群对氯氟氰菊酯的抗性倍数为16倍(Wang et al., 2019)。全国农业技术推广服务中心组织的有害生物抗药性监测结果

(张帅, 2017; 2018; 2019; 2020; 2021)表明, 2016—2020年, 华北地区棉铃虫对三氟氯氰菊酯和辛硫磷表现为中等至高水平抗性, 且在2020年抗性倍数上升明显, 对氯虫苯甲酰胺表现为中等水平抗性, 对茚虫威表现为中等至高水平抗性, 而华北棉区、长江中下游棉区和新疆棉区棉铃虫对甲氨基阿维菌素苯甲酸盐均表现为敏感至低水平抗性(表1)。综上所述

述, 我国华北和长江流域棉区棉铃虫对拟除虫菊酯类杀虫剂抗性水平普遍较高, 但对甲氨基阿维菌素苯甲酸盐等新型药剂仍较敏感, 建议重点在华北棉区开展棉铃虫抗药性治理, 在高水平抗性棉区应停止使用拟除虫菊酯类药剂, 交替轮换使用大环内酯类、恶二嗪类和双酰胺类等不同作用机理的农药, 以提高杀虫剂对棉铃虫的防治效果并延缓抗药性发展。

表1 2016—2020年我国不同棉区棉铃虫对化学杀虫剂的抗性监测结果(张帅, 2017; 2018; 2019; 2020; 2021)

Table 1 Resistance monitoring results in *Helicoverpa armigera* to chemical insecticides in different cotton production areas of China during 2016—2020 (Zhang, 2017; 2018; 2019; 2020; 2021)

杀虫剂 Insecticide	抗性监测地点 Resistance monitoring sites	抗性倍数 Resistance ratio				
		2016	2017	2018	2019	2020
三氟氯氰菊酯 Cyhalothrin	华北棉区 North China cotton areas	21.0–166.0	59.0–269.0	58.0–192.0	42.0–216.0	113.0–342.0
	长江流域棉区 Yangtze River basin cotton areas	5.2–9.8	2.5–9.5	6.2–13.0	14.0–28.0	8.9–16.0
	新疆棉区 Xinjiang cotton areas	–	2.5–9.5	≤5.0	≤5.0	–
辛硫磷 Phoxim	华北棉区 North China cotton areas	15.0–66.0	24.0–29.0	23.0–57.0	20.0–39.0	29.0–68.0
	长江流域棉区 Yangtze River basin cotton areas	15.0–66.0	1.0–2.7	6.7–8.9	3.0–6.0	3.2–5.1
	新疆棉区 Xinjiang cotton areas	6.5–8.5	1.0–2.7	≤5.0	≤5.0	–
甲氨基阿维菌素 苯甲酸盐 Avermectin benzoate	华北棉区 North China cotton areas	10.0–93.0	11.0–90.0	6.8–40.0	7.4–37.0	1.0–4.8
	长江流域棉区 Yangtze River basin cotton areas	10.0–93.0	1.0–1.1	≤5.0	≤5.0	1.0–4.8
	新疆棉区 Xinjiang cotton areas	5.8–8.4	1.0–1.1	≤5.0	≤5.0	–
氯虫苯甲酰胺 Chlorantraniliprole	华北棉区 North China cotton areas	–	–	–	–	5.5–7.2
茚虫威 Indoxacarb	华北棉区 North China cotton areas	–	–	–	–	8.1–56.0

2 解毒酶代谢能力增强引起棉铃虫抗药性

昆虫体内能够代谢杀虫剂等外源物质的解毒酶系主要包括细胞色素 P450 酶系 (cytochrome P450, P450)、羧酸酯酶 (carboxylesterases, CarE)、谷胱甘肽 S-转移酶 (glutathione S-transferases, GST) 和 ATP 结合盒 (ATP-binding cassette, ABC) 转运蛋白 (图 1)。解毒酶活性增强可提高棉铃虫对杀虫剂的解毒代谢能力从而产生抗药性 (Panini et al., 2016)。其中 P450 介导的代谢能力增强是棉铃虫抗药性的主要机制 (Feyereisen, 2012; Feyereisen et al., 2015), 国内外学者对该机制研究较为深入, 对此本文将作重点阐述。

2.1 P450 介导的棉铃虫抗药性

P450 存在于从原核生物到真核生物的几乎所有类型生物体中, 不仅能参与许多内源性物质的合成或分解, 还能催化包括杀虫剂在内的外源性物质解毒代谢 (邱星辉, 2014; Lu et al., 2021), 其活性增强已被证实是很多昆虫对杀虫剂产生抗性的重要原因 (Soderlund et al., 1989; Scott, 1999; Khan et al., 2020)。P450 介导棉铃虫抗药性的分子机制主要包括 P450 基因过量表达、氨基酸残基改变以及两者的

联合作用。

2.1.1 P450 基因组成型过量表达

P450 基因组成型过量表达以及代谢能力增强是昆虫抗药性发展过程中的常见现象 (Feyereisen, 2011; Chen et al., 2018)。越来越多的研究表明, 单个或多个 P450 基因的过量表达参与了棉铃虫对杀虫剂的抗药性。如 Wang & Hobbs (1995) 最早报道了与棉铃虫抗药性相关的 P450 基因 *CYP6B2*; Ranasinghee & Hobbs (1998; 1999) 随后克隆了 *CYP6B6* 和 *CYP6B7* 基因并证明 *CYP6B7* 与棉铃虫对拟除虫菊酯的抗性相关。笔者所在中国农业大学理学院生物测定实验室亦研究发现, *CYP6B7* 基因在棉铃虫抗氰戊菊酯种群中的表达水平显著高于敏感种群 (唐涛等, 2007; Zhang et al., 2010); 利用 RNAi 技术干扰 *CYP6B7* 的表达后, 棉铃虫对氰戊菊酯和高效氯氰菊酯的敏感性增加 (Tang et al., 2012; 2013); 而且在毕赤酵母 *Pichia pastoris* 中异源表达的 *CYP6B7* 蛋白对氰戊菊酯等拟除虫菊酯杀虫剂有代谢活性 (Zhao et al., 2017; 2018), 表明 *CYP6B7* 基因在棉铃虫对氰戊菊酯的抗性中发挥着重要作用。Tian et al. (2017) 在大肠杆菌 *Escherichia coli* 中共表达 *CYP6B6*

和 P450 还原酶 HaCPR, 发现 CYP6B6 能将氰戊菊酯代谢为无毒的 4'-羟基氰戊菊酯, 表明 CYP6B6 基因也在棉铃虫对氰戊菊酯的解毒代谢中起重要作用。在非洲和欧洲国家抗溴氰菊酯的棉铃虫以及中国东北地区抗 λ -氯氟氰菊酯的棉铃虫中均检测到 CYP6AE11 基因的过量表达 (Brun-Barale et al., 2010; Wang et al., 2019)。对棉铃虫 CYP6AE 亚家族的 10 个 P450 基因进行功能研究, 发现 10 个 CYP6AE 基因中有 9 个异源表达后将氰戊菊酯代谢为无毒的 4'-羟基氰戊菊酯, 其中 CYP6AE11、CYP6AE14 和 CYP6AE17 蛋白的代谢能力最高 (Shi et al., 2018), 此外, CYP6AE17 和 CYP6AE18 蛋白还具有代谢茚虫威的能力 (Wang et al., 2018)。CYP9A12、CYP9A14 和 CYP9A17v2 基因在棉铃虫抗性种群中也过量表达 (Yang et al., 2006; 杨亦桦等, 2009; 陈爱华等, 2012), 而且在酿酒酵母 *Saccharomyces cerevisiae* 中异源表达的 CYP9A12、CYP9A14 和 CYP9A17v2 蛋白能够代谢包括顺式氰戊菊酯在内的拟除虫菊酯类杀虫剂, 表明这些 P450 基因参与了棉铃虫对菊酯类杀虫剂的抗性 (Yang et al., 2008; 杨亦桦等, 2009)。Wee et al. (2008) 通过 cDNA-扩增片段长度多态性 (amplified fragment length poly-

morphism, AFLP) 方法鉴定了 4 个候选解毒酶基因, 发现 CYP337B1 基因在澳大利亚抗氰戊菊酯棉铃虫 AN02 种群中过量表达, 而且该基因与氰戊菊酯抗性位点 *RFen1* 紧密相关, 表明 CYP337B1 基因可能与氰戊菊酯解毒代谢有关。而 CYP337B3 是由 2 个亲本 P450 基因 CYP337B1 和 CYP337B2 之间不平衡杂交而产生的一种嵌合酶, 能将氰戊菊酯代谢为无毒的 4'-羟基氰戊菊酯 (Joußen et al., 2012); 随后的研究表明, 这种机制也存在于巴基斯坦抗氯氰菊酯棉铃虫 FSD 种群中, 在昆虫细胞 Ha2302 中异源表达的 CYP337B3 蛋白能将氯氰菊酯代谢为无毒的 4'-羟基氯氰菊酯 (Rasool et al., 2014)。Xu et al. (2016) 研究还发现, 多个 P450 基因 CYP332A1、CYP4L11、CYP4L5、CYP4M6、CYP4M7、CYP6B7、CYP9A12 和 CYP9A14 在我国北方田间抗氰戊菊酯棉铃虫中过量表达。类似地, CYP4L5、CYP4L11、CYP6AE11、CYP332A1 和 CYP9A14 基因在抗溴氰菊酯棉铃虫种群中也过量表达 (Brun-Barale et al., 2010); 而 CYP9A14、CYP9A17、CYP9G5、CYP9A3、CYP6AE11、CYP6B7、CYP6AB9 和 CYP6B8 基因过量表达在棉铃虫对 λ -氯氟氰菊酯的抗性中发挥着重要作用 (Wang et al., 2019)。

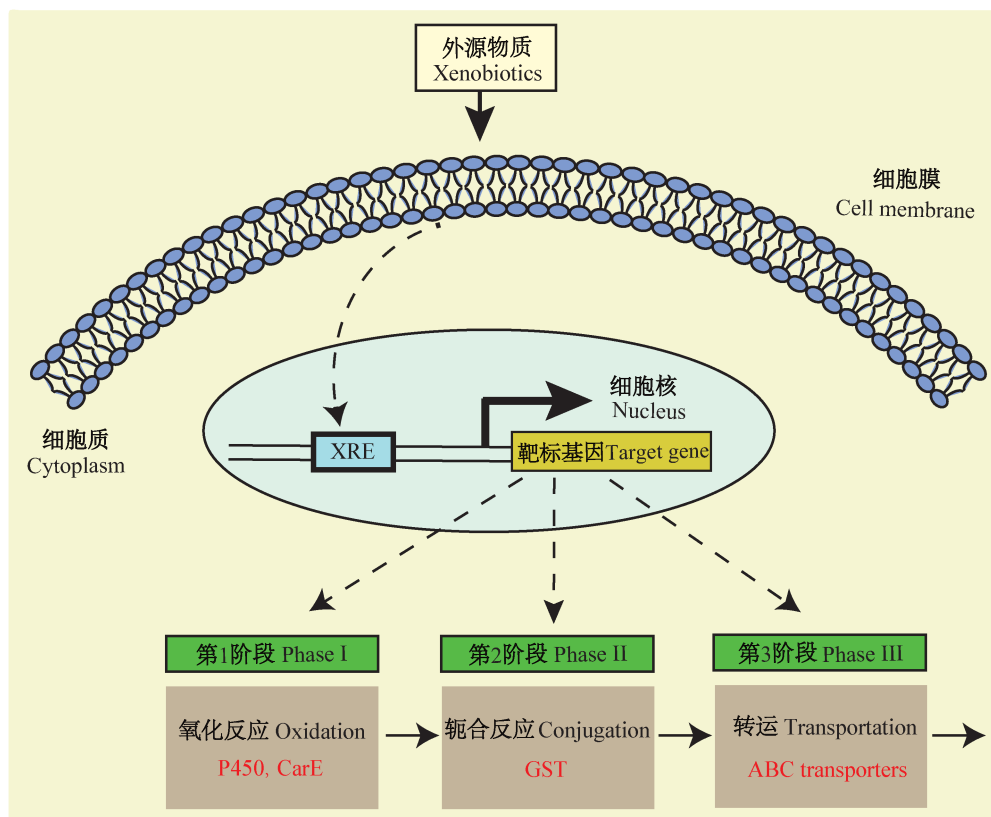


图1 外源化合物代谢途径示意图(改编自 Ye et al., 2022)

Fig. 1 Schematic diagram of metabolic pathway for xenobiotic compounds (Adapted from Ye et al., 2022)

2.1.2 P450基因诱导型过量表达

可诱导性是P450基因的一个重要特征(Scott et al., 1996; Mao et al., 2007)。P450基因的诱导表达和组成型过量表达都被认为在昆虫对杀虫剂的抗性中起着重要作用(Feyereisen, 2011; Liu NN et al., 2015)。Huang et al.(2021)研究发现,棉铃虫 *CYP6B7* 基因能被氰戊菊酯、辛硫磷和茚虫威显著诱导上调表达。此外, Tao et al.(2012)发现棉酚和花椒毒素能显著诱导 *CYP6B7* 等基因的表达,而且棉酚诱导的多个P450基因有助于提高棉铃虫对溴氰菊酯的耐受性。棉铃虫 *CYP6B6* 基因表达水平能被槲皮素和溴氰菊酯显著诱导(Liu D et al., 2015; Zhou et al., 2010),而沉默 *CYP6B6* 基因的表达能降低其对联苯菊酯、3-氟氯氰菊酯和毒死蜱的耐受性(Zhao et al., 2016)。槲皮素能介导 *CYP6B6*、*CYP6B8* 和 *CYP321A1* 基因的上调表达从而降低棉铃虫对 λ -氯氟氰菊酯的敏感性(Chen et al., 2018)。柠檬烯、橙花醇、2-庚酮、乙酸顺-3-己烯酯4种植物挥发性化

物和黄酮、香豆素、丁布、齿阿米素4种植物化感物质均能诱导P450基因 *CYP6B2*、*CYP6B6* 和 *CYP6B7* 的表达,从而提高棉铃虫对灭多威的耐受性(Chen et al., 2019; Wu et al., 2021)。以上研究均表明, P450基因能被杀虫剂及其他外源物质诱导表达,从而提高棉铃虫对杀虫剂及其他外源物质的耐受性。

2.1.3 P450基因氨基酸残基突变

除了P450基因的过量表达,氨基酸残基突变也能增强P450基因对杀虫剂的解毒代谢活性,从而促进棉铃虫对杀虫剂的抗性。如赵伊英等(2012)报道石河子市棉区棉铃虫抗性种群的 *CYP6AE14* 基因存在1个氨基酸突变位点Y25F,这种突变可能与棉铃虫对棉酚及杀虫剂的抗性有关。Zhang et al.(2010)研究也发现,与棉铃虫敏感种群相比, *CYP6B7* 基因在氰戊菊酯抗性种群中除了过量表达外,还存在3个氨基酸残基突变位点V144M、E256K 和 C319Y,表明 *CYP6B7* 基因过量表达与其氨基酸残基突变共同在棉铃虫对氰戊菊酯的抗性中发挥着重要作用。

表2 细胞色素P450介导的棉铃虫对杀虫剂的代谢抗性分子机制

Table 2 Cytochrome P450 mediated metabolic resistance mechanisms in *Helicoverpa armigera* to insecticides

P450基因 P450 gene	抗药性机制 Resistance mechanism	参考文献 Reference
<i>CYP6B7</i> , <i>CYP337B1</i>	P450基因组型过量表达介导棉铃虫对氰戊菊酯的抗性 Constitutive overexpression of P450 genes mediates the resistance of <i>H. armigera</i> to fenvalerate	Ranasinghe & Hobbs, 1998; 1999; Zhang et al., 2010; Tang et al., 2012; Zhao et al., 2017; Wee et al., 2008
<i>CYP6AE11</i>	P450基因组型过量表达介导棉铃虫对 λ -氯氟氰菊酯的抗性 Constitutive overexpression of P450 genes mediates the resistance of <i>H. armigera</i> to lambda-cyhalothrin	Brun-Barale et al., 2010
<i>CYP332A1</i> , <i>CYP4L11</i> , <i>CYP4L5</i> , <i>CYP4M6</i> , <i>CYP4M7</i> , <i>CYP6B7</i> , <i>CYP9A12</i> , <i>CYP9A14</i>	P450基因组型过量表达介导棉铃虫对氰戊菊酯的抗性 Constitutive overexpression of P450 genes mediates the resistance of <i>H. armigera</i> to fenvalerate	Xu et al., 2016
<i>CYP4L5</i> , <i>CYP4L11</i> , <i>CYP6AE11</i> , <i>CYP332A1</i> , <i>CYP9A14</i>	P450基因组型过量表达介导棉铃虫对溴氰菊酯的抗性 Constitutive overexpression of P450 genes mediates the resistance of <i>H. armigera</i> to deltamethrin	Brun-Barale et al., 2010
<i>CYP9A14</i> , <i>CYP9A17</i> , <i>CYP9G5</i> , <i>CYP9A3</i> , <i>CYP6AE11</i> , <i>CYP6B7</i> , <i>CYP6AB9</i> , <i>CYP6B8</i>	P450基因组型过量表达介导棉铃虫对 λ -氯氟氰菊酯的抗性 Constitutive overexpression of P450 genes mediates the resistance of <i>H. armigera</i> to lambda-cyhalothrin	Wang et al., 2019
<i>CYP337B3</i>	异源表达P450对氰戊菊酯和氯氟氰菊酯具有解毒代谢能力 Metabolic detoxification of fenvalerate and cypermethrin are induced by heterologously expressed P450	JouBen et al., 2012; Rasool et al., 2014
<i>CYP6AE11</i> , <i>CYP6AE12</i> , <i>CYP6AE14</i> , <i>CYP6AE15</i> , <i>CYP6AE16</i> , <i>CYP6AE17</i> , <i>CYP6AE18</i> , <i>CYP6AE19</i> , <i>CYP6AE24</i> , <i>CYP6B6</i>	异源表达P450对氰戊菊酯具有解毒代谢能力 Metabolic detoxification of fenvalerate is induced by heterologously expressed P450	Shi et al., 2018; Tian et al., 2017
<i>CYP6AE17</i> , <i>CYP6AE18</i>	异源表达P450对茚虫威具有解毒代谢能力 Metabolic detoxification of indoxacarb is induced by heterologously expressed P450	Wang et al., 2018
<i>CYP6B8</i> , <i>CYP321A1</i>	异源表达P450对艾氏剂、氯氟氰菊酯和二嗪农有解毒代谢能力 Metabolic detoxification of aldrin, cypermethrin and diazinon are induced by heterologously expressed P450	Sasabe et al., 2004; Rupasinghe et al., 2007

续表2 Continued

P450 基因 P450 gene	抗药性机制 Resistance mechanism	参考文献 Reference
<i>CYP9A12</i> , <i>CYP9A14</i> , <i>CYP9A17v2</i>	P450 基因组成型过量表达介导棉铃虫对顺式氰戊菊酯的抗性,且异源表达 P450 对顺式氰戊菊酯具有解毒代谢能力 Constitutive overexpression of P450 genes mediates the resistance in <i>H. armigera</i> to esfenvalerate, and metabolic detoxification of esfenvalerate is induced by heterologously expressed P450	Yang et al., 2006; 2008; 杨亦桦等, 2009; 陈爱华等, 2012
<i>CYP6B7</i>	P450 基因诱导表达可提高棉铃虫对氰戊菊酯、辛硫磷和茚虫威的耐受性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to fenvalerate, phoxim and indoxacarb	Yang et al., 2006; 2008; 2009; Chen et al., 2012 Huang et al., 2021
<i>CYP6B6</i>	P450 基因诱导表达提高棉铃虫对溴氰菊酯的耐受性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to deltamethrin	Liu D et al., 2015; Zhou et al., 2010
<i>CYP321A1</i>	P450 基因诱导表达提高棉铃虫对氯氰菊酯的耐受性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to cypermethrin	Sasabe et al., 2004
<i>CYP6B2</i> , <i>CYP6B6</i> , <i>CYP6B7</i>	P450 基因诱导表达提高棉铃虫对灭多威的耐受性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to methomyl	Chen et al., 2019; Wu et al., 2021
<i>CYP6B6</i> , <i>CYP6B8</i> , <i>CYP321A1</i>	P450 基因诱导表达提高棉铃虫对 λ -氯氟氰菊酯的耐受性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to lambda-cyhalothrin	Chen et al., 2018
<i>CYP321A1</i> , <i>CYP9A12</i> , <i>CYP9A14</i> , <i>CYP6AE11</i> , <i>CYP6B7</i>	P450 基因诱导表达提高棉铃虫对溴氰菊酯的耐受性,而且沉默 <i>CYP9A14</i> 基因提高棉铃虫对溴氰菊酯的敏感性 Induced expression of P450 genes increases the tolerance of <i>H. armigera</i> to deltamethrin, and silencing of <i>CYP9A14</i> gene increases the sensitivity of <i>H. armigera</i> to deltamethrin	Tao et al., 2012
<i>CYP6B6</i>	沉默 P450 基因提高棉铃虫对联苯菊酯、3-氟氯氰菊酯和毒死蜱的敏感性 Silencing of P450 gene increases the sensitivity in <i>H. armigera</i> to bifenthrin, 3-cyhalothrin and chlorpyrifos	Zhao et al., 2016
<i>CYP6AE14</i>	P450 基因氨基酸残基突变介导棉铃虫对拟除虫菊酯类杀虫剂的抗性 Amino acid residue mutation of P450 gene mediates the resistance in <i>H. armigera</i> to pyrethroid insecticides	赵伊英等, 2012 Zhao et al., 2012
<i>CYP6B7</i>	P450 基因过量表达与氨基酸残基突变联合作用介导棉铃虫对氰戊菊酯的抗性 Combination of P450 gene overexpression and amino acid residue mutation mediate the resistance in <i>H. armigera</i> to fenvalerate	Zhang et al., 2010

2.1.4 P450 基因表达调控机制

真核生物基因表达受基因组、转录、转录后、翻译以及翻译后等不同水平的调控。其中转录水平调控是控制基因表达的关键(Kranthi et al., 2002),而转录因子和顺式作用元件相互作用是该水平调控的分子基础(Harshman & James, 1998;唐振华和吴士雄, 2000)。昆虫 P450 基因的表达可能受顺式作用元件、转录因子以及顺式作用元件和转录因子的共同调控(Li et al., 2002; Liu NN et al., 2015)。周颖君等(2008)利用基因组步移技术克隆了棉铃虫 *CYP9A12* 基因的 5'侧翼序列并对其进行生物信息学分析,发现该序列包含启动子核心结构序列、GATA-1

和 Dfd 等转录因子结合位点。严宇澄等(2009)克隆了棉铃虫 *CYP9A17v2* 基因的 5'侧翼序列并构建了含 *CYP9A17v2* 启动子不同长度的荧光素酶报告基因,检测发现所有不同长度构建子均具有启动子活性,但活性强弱不同,其中-197 bp 到+43 bp 区域的转录活性最高,推测-197 bp 到-113 bp 区域内存在转录增强因子的结合位点。2-十三烷酮能诱导棉铃虫 *CYP6B6* 基因的过量表达(于彩虹等, 2002; Liu et al., 2006); Li et al.(2014)克隆了 *CYP6B6* 基因的 5'侧翼序列并构建了报告基因,经双荧光素酶活性检测发现 *CYP6B6* 启动子-373 bp 到-172 bp 区域对 *CYP6B6* 的转录激活非常重要,进一步通过凝胶电泳

迁移率变动分析发现-373 bp到-172 bp区域能特异性结合核因子并调节激活域的活性,最终确定棉铃虫 *CYP6B6* 启动子中2-十三烷酮的响应区在-292 bp和-154 bp之间;随后 Zhao et al.(2016)以2-十三烷酮响应区的保守序列作为诱饵,利用酵母单杂交技术筛选到2个可以和 *CYP6B6* 启动子中2-十三烷酮响应区结合的潜在转录因子,通过NCBI数据库比对发现其中1个候选转录因子与家蚕 *Bombyx mori* FK506结合蛋白(FK506 binding protein, FKBP)同源,属于FKBP-C超家族。FKBP是原核细胞和真核细胞中免疫抑制剂FK506蛋白的天然同源受体,可以催化N端脯氨酸残基从顺式到反式的构象,从而影响蛋白质的活性、磷酸化、蛋白质-蛋白质相互作用、亚细胞定位以及蛋白质底物的稳定性(Yan et al., 2014)。此外,Zhao et al.(2020)通过酵母单杂交技术还筛选到另一个转录因子乙醇脱氢酶5(alcohol dehydrogenase 5, ADH5),该转录因子能和 *CYP6B6* 启动子中2-十三烷酮响应区HE1元件(-373 bp~+21 bp)结合,调控 *CYP6B6* 基因的表达从而响应2-十三烷酮的毒性作用。Xu et al.(2018)也发现2-十三烷酮能诱导棉铃虫 *CYP6B7* 基因的过量表达,并鉴定到棉铃虫 *CYP6B7* 启动子中2-十三烷酮的响应区在-280 bp和-257 bp之间。以上研究结果可为深入探究棉铃虫P450基因表达调控机制以及其参与杀虫剂抗性的分子机制奠定基础。

2.2 CarE介导的棉铃虫抗药性

CarE作为一种重要的解毒代谢酶,也在昆虫抗药性中起着重要作用(Li et al., 2007; Farnsworth et al., 2010)。董利霞等(2011)研究表明,棉铃虫对甲氨基阿维菌素苯甲酸盐的敏感性降低与CarE比活力增强有关,而且亚致死剂量的甲氨基阿维菌素苯甲酸盐对棉铃虫CarE活性具有一定诱导作用。Wu et al.(2011)研究发现,CarE基因 *CCE001a*、*CCE001i* 和 *CCE001j* 在棉铃虫抗性种群中的组成型过量表达可能与氰戊菊酯抗性有关。Bai et al.(2019)在棉铃虫敏感品系中克隆得到1条长为2 244 bp的 *CarE001G*,将其在大肠杆菌中表达后发现纯化蛋白可代谢 β -氯氰菊酯、 λ -氯氰菊酯和氰戊菊酯,对其C端富含甘氨酸区域进行缺失后能显著增强CarE001G蛋白对 β -氯氰菊酯的代谢能力(Bai et al., 2021)。此外,在大肠杆菌中重组表达的棉铃虫CarE001A和CarE001H蛋白对 α -萘乙酸具有较高的代谢活性,而且能够代谢 β -氯氰菊酯和 λ -氯氰菊酯(Li et al., 2020)。棉铃虫CarE001D蛋白对 β -氯

氰菊酯和氰戊菊酯也有一定的代谢活性(Li et al., 2016)。在槲皮素喂养的棉铃虫中,CarE活性及其对 λ -三氟氯氰菊酯水解代谢能力的增强,有助于提高棉铃虫对 λ -三氟氯氰菊酯的耐受性(Chen et al., 2017)。

CarE突变也可导致棉铃虫产生抗药性,如第137位点甘氨酸到天冬氨酸的突变使棉铃虫对有机磷的水解活性增加约14倍,而第251位点色氨酸到亮氨酸的突变使其对氰戊菊酯和氯氰菊酯的水解活性增加4~6倍,这些突变可能与棉铃虫对有机磷和拟除虫菊酯的抗性有关(Li et al., 2013)。而棉铃虫CarE001C蛋白中第432位点组氨酸到异亮氨酸的突变和第322位点精氨酸到亮氨酸的突变能显著提高棉铃虫对氰戊菊酯的水解活性,表明这2个突变可能引起了棉铃虫对氰戊菊酯的抗性(Xu JJ et al., 2021)。以上研究表明,CarE在棉铃虫对拟除虫菊酯等杀虫剂的解毒代谢及抗性中发挥着重要作用。

2.3 GST介导的棉铃虫抗药性

GST通过共轭作用与昆虫体内杀虫剂结合,将杀虫剂降解为巯基尿酸类物质排出体外,主要参与有机磷和拟除虫菊酯类杀虫剂的解毒代谢。徐希宝等(2014)研究发现棉铃虫对甲氧虫酰肼的抗性与GST比活力增强有关,而GST比活力增强主要与 *GSTd1*、*GSTd2*、*GSTe1* 和 *GSTs1* 过量表达有关;而且利用RNAi技术干扰GST基因的表达,能降低GST的活性并提高棉铃虫对甲氧虫酰肼的敏感性(徐希宝等, 2015)。王芹芹等(2017)发现河北省邯郸市棉铃虫种群对茚虫威产生中等水平抗性与其体内GST活性显著提高有关。而且 *GSTs1* 和 *GSTd1* 的过量表达与棉铃虫田间种群对茚虫威的抗性水平呈正相关(Wang et al., 2021)。毒死蜱、敌敌畏、氯氰菊酯暴露均能引起棉铃虫GST活性增强和GST基因表达水平上调,将 *HaGST-8* 基因在毕赤酵母中异源表达,发现其重组蛋白能有效代谢毒死蜱、敌敌畏和氯氰菊酯(Labade et al., 2018),但 *HaGST-8* 与棉铃虫抗药性的关系仍有待进一步研究验证。

2.4 ABC转运蛋白介导的棉铃虫抗药性

ABC转运蛋白为跨膜蛋白,可利用ATP水解产生的能量对杀虫剂进行跨膜运输,最终排出体外。有关ABC转运蛋白与杀虫剂抗性关系的研究,目前在黑腹果蝇 *Drosophila melanogaster* (Denecke et al., 2017; Xu HQ et al., 2021)、烟粉虱 *Bemisia tabaci* (Yang et al., 2013)、赤拟谷盗 *Tribolium castaneum* (Broehan et al., 2013)以及埃及伊蚊 *Aedes aegypti*

(Bariami et al., 2012)等昆虫中报道较多,在棉铃虫中的研究则较少。Srinivas et al.(2004)和 Aurade et al.(2010)曾报道,由 ABCB 亚家族编码的 P-糖蛋白表达量升高可能是棉铃虫对拟除虫菊酯和有机磷类杀虫剂产生抗性的原因之一。Jin et al.(2019)研究发现,暴露于茚虫威、阿维菌素和 λ -氯氟氰菊酯中,棉铃虫 ABCG 亚家族的 *HaOG200310*、*HaOG200353* 和 *HaOG200354* 基因的表达量显著上调,表明 *HaOG200310*、*HaOG200353* 和 *HaOG200354* 蛋白可能参与茚虫威、阿维菌素和 λ -氯氟氰菊酯的代谢。此外,棉酚可显著诱导棉铃虫幼虫 *HaABCB6* 基因表达,利用 CRISPR/Cas9 技术敲除 *HaABCB6* 基因后,棉铃虫对棉酚的敏感性显著增加,表明 *HaABCB6* 蛋白在棉酚解毒代谢中起着重要作用(Jin et al., 2020)。

3 靶标敏感性降低引起棉铃虫抗药性

杀虫剂的作用靶标主要包括乙酰胆碱受体(acetylcholine receptor, AChR)、乙酰胆碱酯酶(acetylcholinesterase, AChE)、钠离子通道和 γ -氨基丁酸(γ -amniobutyric acid, GABA)受体等。大量研究表明,作用靶标敏感性下降是昆虫产生抗药性的重要机制(Ffranch-Constant., 1999;封云涛等,2009)。

AChR 是神经递质门控的离子通道蛋白,主要负责神经系统突触间兴奋递质的传递,是多杀菌素和新烟碱类杀虫剂的作用靶标(Brown et al., 2006)。Wang et al.(2020a)研究发现,与棉铃虫野生型亲本 SCD 种群相比,利用 CRISPR/Cas9 技术敲除棉铃虫 AChR alpha 6 亚基后的种群 alpha 6-KO 对多杀菌素和乙基多杀菌素分别产生了 531 倍和 1 105 倍的抗性,表明 alpha 6 亚基是棉铃虫中多杀菌素的靶标位点。

AChE 是有机磷和氨基甲酸酯类杀虫剂的作用靶标,这 2 类杀虫剂与 AChE 结合可使酶催化部位发生磷酸化和氨基甲酰化而失活,从而破坏正常神经传导,使害虫长期处于神经兴奋状态,最终导致死亡(Fournier & Mutero, 1994;Gunning et al., 1998;Gunning, 2006)。与棉铃虫敏感品系相比,抗性品系的 AChE 对久效磷和甲基对氧磷的敏感性显著下降,表明 AChE 敏感性降低可能是棉铃虫对该杀虫剂产生抗性的重要原因(Srinivas et al., 2004)。分析比对棉铃虫抗性品系和敏感品系的 AChE 基因全序列,发现存在 9 个氨基酸突变位点,其中第 585 位点丙氨酸/苏氨酸突变可能是造成棉铃虫 AChE 对久效磷敏感性下降的原因(Ren et al., 2002)。

钠离子通道是细胞质膜上的跨膜糖蛋白,主要维持细胞兴奋和传导,是有机氯和拟除虫菊酯类杀虫剂的重要靶标位点。钠离子通道基因突变可降低其与有机氯、拟除虫菊酯类杀虫剂的亲和性,从而产生击倒抗性(West & McCaffery, 1992;Dong, 2007)。Head et al.(1998)研究发现,棉铃虫抗性品系 para 型钠离子通道 III 和 IV 结构域第 1 561 位点存在天冬氨酸到缬氨酸的突变,第 1 565 位点存在谷氨酸到甘氨酸的突变,这些突变可能与棉铃虫对氯氰菊酯的抗性有关。类似地,王桂荣等(2004)研究抗溴氰菊酯棉铃虫钠离子通道 II~IV 结构域序列,发现第 223 位点和第 530 位点的甲硫氨酸分别突变为亮氨酸和缬氨酸,认为这 2 个突变位点很可能与棉铃虫对溴氰菊酯的抗性有关。

GABA 受体为环戊二烯类杀虫剂作用靶标。Wang et al.(2020b)利用 CRISPR/Cas9 技术敲除棉铃虫中编码 GABA 受体 Rdl 亚基 *HaRdl-1* 和 *HaRdl-2* 基因,结果发现,与棉铃虫敏感品系相比,敲除 *HaRdl-1* 的棉铃虫对硫丹、艾氏剂和狄氏剂的抗性显著增加,而敲除 *HaRdl-2* 的棉铃虫对这 3 种环戊二烯类杀虫剂的抗性减弱,说明 *HaRdl-1* 和 *HaRdl-2* 都在棉铃虫对 2 种环戊二烯类杀虫剂的抗性中起着重要作用,但作用相反。由于 *Rdl-1* 和 *Rdl-2* 基因在 Z 染色体第 302 位上分别编码丙氨酸和丝氨酸,因此推测棉铃虫可能通过 *HaRdl-1* 的 Ala302Ser 突变或 *HaRdl-2* 的表达增强从而介导棉铃虫对环戊二烯类杀虫剂的抗性。此外,棉铃虫 *HaRdl-1* 敲除品系对阿维菌素的敏感性降低 2.3 倍,但对氟虫腴的敏感性无明显变化;而棉铃虫 *HaRdl-2* 敲除品系对氟虫腴的敏感性提高 2.1 倍,但对阿维菌素的敏感性无变化,推测 *HaRdl-1* 和 *HaRdl-2* 能在一定程度上介导棉铃虫对阿维菌素和氟虫腴的敏感性(Wang et al., 2020b)。

4 表皮穿透能力下降引起棉铃虫抗药性

表皮穿透能力下降可延缓杀虫剂到达靶标位点的时间,使昆虫能充分降解代谢进入体内的杀虫剂,减少到达靶标部位的药量,从而产生抗药性(孙雅雯和郑彬, 2015;Balabanidou et al., 2018)。值得注意的是,表皮穿透性降低单独作用通常不会引起很高水平的抗性,但与代谢抗性共同作用可使害虫抗性水平显著提高。如 Ahmad et al.(2006)发现以 ^{14}C 标记的溴氰菊酯点滴处理棉铃虫,50% 的溴氰菊酯穿透表皮进入棉铃虫抗性种群的时间为 6 h,而进入棉

铃虫敏感种群的时间仅为1 h;处理48 h后敏感种群体内仍有40%的溴氰菊酯残留,抗性种群中溴氰菊酯残留量不足14%,而且抗性种群排泄物中脂溶性代谢物几乎是敏感种群的2倍,表明表皮穿透能力下降和代谢能力增强是棉铃虫对溴氰菊酯产生抗性的重要机制。张万娜等(2021)以甲氧虫酰肼处理棉铃虫后,试虫表皮蛋白基因CP22和CPI4的相对表达水平显著上调,表明棉铃虫CP22和CPI4基因能响应甲氧虫酰肼的胁迫,认为该表皮基因可作为棉铃虫对甲氧虫酰肼抗性治理的潜在靶标。

5 展望

为保障粮食增产丰收,化学防治仍是田间害虫防控的重要手段。棉铃虫对化学杀虫剂的抗性不容忽视并亟待解决。传统的抗药性治理策略主要是从用药不当引起抗性方面考虑,采用不同种类、不同作用方式杀虫剂进行合理混用、或轮换使用新型高效杀虫剂、在棉铃虫敏感时期用药等方法,可提高药剂对棉铃虫的防治效果,并能在一定程度上延缓抗药性的发展。在传统综合抗药性治理的基础上,仍需进一步了解抗药性产生的内在分子机制,寻求更直接有效的抗药性治理新技术,才有可能真正解决棉铃虫抗药性问题。

目前,棉铃虫对杀虫剂抗性的分子机制研究已取得一定进展,其中以解毒酶介导的杀虫剂解毒代谢能力增强的研究最为深入。但由于解毒酶种类的多样性以及功能机制的复杂性,大多数研究主要集中在解毒酶基因过量表达以及对杀虫剂降解代谢检测上,较少涉及棉铃虫解毒酶基因表达调控分子机制。近年来,随着高通量测序技术、各种组学以及生物信息学技术的快速发展,分子生物学与生物化学等功能研究手段的革新,一些昆虫解毒酶基因调控分子机制的研究取得了重要进展。以P450解毒酶系为例,在转录水平上已鉴定出参与赤拟谷盗(Kalsi & Palli, 2017)、烟粉虱(Yang et al., 2020)、致倦库蚊*Culex quinquefasciatus*(Li & Liu, 2017)和甜菜夜蛾*Spodoptera exigua*(Hu et al., 2021)等昆虫抗药性的P450基因调控途径;在转录后水平上也已发现一些非编码RNA,如miRNA能调控抗性昆虫P450基因的表达(Tian et al., 2016; Guo et al., 2017; Sun et al., 2019),这些研究结果为深入探究棉铃虫抗药性相关解毒酶基因,尤其是P450基因的表达调控分子机制提供了参考。此外,随着科学技术的发展,以有害生物靶标基因为导向研制核酸农药已成为可能

(王治文等, 2019),而且通过纳米粒子装载RNAi农药的新技术也日渐成熟(Yan et al., 2021)。未来通过对调控分子机制的深入研究,明确调控解毒酶基因过量表达的信号通路和关键环节,可为设计开发针对棉铃虫抗药性的新型RNAi农药奠定基础,为制订棉铃虫抗药性治理策略提供更多理论依据。

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